

Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution

Highlights

- High-level cortical regions and the thalamus show increased connectivity under LSD
- The brain's modular and rich-club organization is altered under LSD
- Increased global connectivity under LSD correlates with ego dissolution scores

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In Brief

Tagliazucchi et al. find that increased global communication mediated by the brain's key integration centers underlies LSD-induced "ego dissolution." This globally enhanced integration impairs the functional identity of brain systems, leading to feelings of ego dissolution and disturbed ego boundaries.

Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution

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SUMMARY

Lysergic acid diethylamide (LSD) is a non-selective serotonin-receptor agonist that was first synthesized in 1938 and identified as (potently) psychoactive in 1943. Psychedelics have been used by indigenous cultures for millennia [1]; however, because of LSD's unique potency and the timing of its discovery (coinciding with a period of major discovery in psychopharmacology), it is generally regarded as the quintessential contemporary psychedelic [2]. LSD has profound modulatory effects on consciousness and was used extensively in psychological research and psychiatric practice in the 1950s and 1960s [3]. In spite of this, however, there have been no modern human imaging studies of its acute effects on the brain. Here we studied the effects of LSD on intrinsic functional connectivity within the human brain using fMRI. High-level association cortices (partially overlapping with the default-mode, salience, and frontoparietal attention networks) and the thalamus showed increased global connectivity under the drug. The cortical areas showing increased global connectivity overlapped significantly with a map of serotonin 2A (5-HT_{2A}) receptor densities (the key site of action of psychedelic drugs [4]). LSD also increased global integration by inflating the level of communication between normally distinct brain networks. The increase in global connectivity observed under LSD correlated with subjective reports of

"ego dissolution." The present results provide the first evidence that LSD selectively expands global connectivity in the brain, compromising the brain's modular and "rich-club" organization and, simultaneously, the perceptual boundaries between the self and the environment.

RESULTS

We used fMRI to investigate global and local changes in functional connectivity following intravenous injection of lysergic acid diethylamide (LSD) versus placebo to 15 healthy volunteers. The experiment followed a randomized and balanced within-subject design, and both whole-brain exploratory and more selective hypothesis-driven data-analysis approaches were employed. Based on the predominantly cortical distribution of serotonin 2A (5-HT_{2A}) receptors [5, 6] (the principal receptor mediating psychedelic effects [4]), as well as previous findings with other psychedelics [5, 7, 8], we hypothesized that connectivity changes would implicate high-level cortical networks such as the default-mode network (DMN) [9] and salience network [10]. The association between these networks and self-consciousness [7, 11, 12] led us to expect a parametric correlation with the intensity of subjective reports of "ego dissolution" under LSD, i.e., a compromised sense of possessing an integrated and distinct personality or identity.

We first studied changes in the overall connectivity of 401 even-sized regions of interest (ROIs) completely covering cortical and sub-cortical gray matter and obtained using a method introduced by Zalesky and colleagues [13]. We computed the functional connectivity density (FCD) [14] as the average correlation

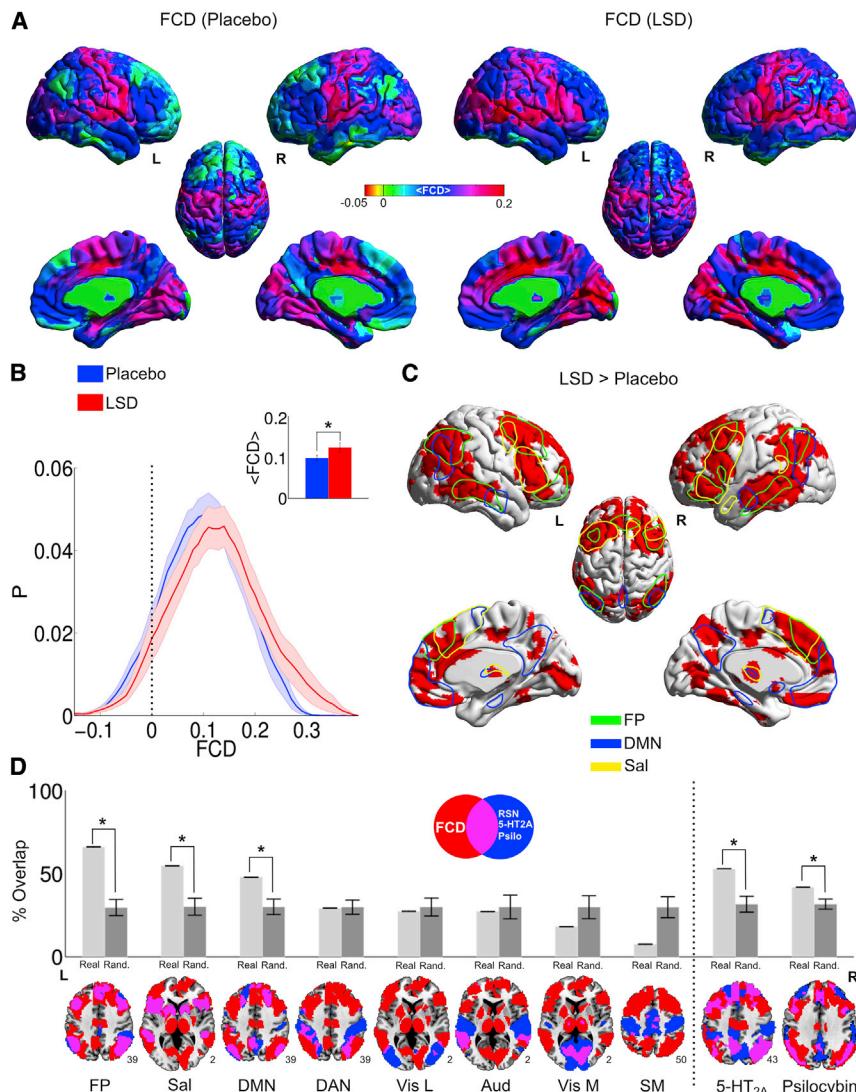


Figure 1. LSD Selectively Increases Global Functional Connectivity of Higher-Level Integrative Cortical and Sub-cortical Regions

(A) Average FCD under the placebo and LSD conditions.

(B) Normalized histogram (P) of all FCD values for both conditions (mean \pm SEM). The inset shows the whole-brain FCD averages ($*p < 0.05$, two-tailed t test).

(C) Rendering of significant FCD increases under LSD versus placebo (thresholded at $p < 0.05$, two-tailed t test, false discovery rate [FDR]-controlled for multiple comparisons). Outlines of the bilateral frontoparietal, salience, and default-mode RSN are overlaid on top of the map of FCD significant increases.

(D) Quantitative analysis of the overlap between significant FCD increases and eight RSNs (FP, frontoparietal; Sal, salience; DMN, default-mode network; DAN, dorsal attention network; Vis L, lateral visual; Aud, auditory; Vis M, medial visual; SM, sensorimotor) obtained from 35 subjects scanned in the Human Connectome Project, as well as 5-HT_{2A} receptor concentration and FCD increases under psilocybin. Only FP, Sal, DMN, and the maps of 5-HT_{2A} receptor concentration and FCD increases under psilocybin had an overlap significantly greater than that observed when spatially randomizing the networks (mean \pm SD, $*p < 0.05$, Bonferroni corrected for multiple comparisons). For a description of the randomization procedure, see [15] and the [Supplemental Experimental Procedures](#). See also [Figure S1](#).

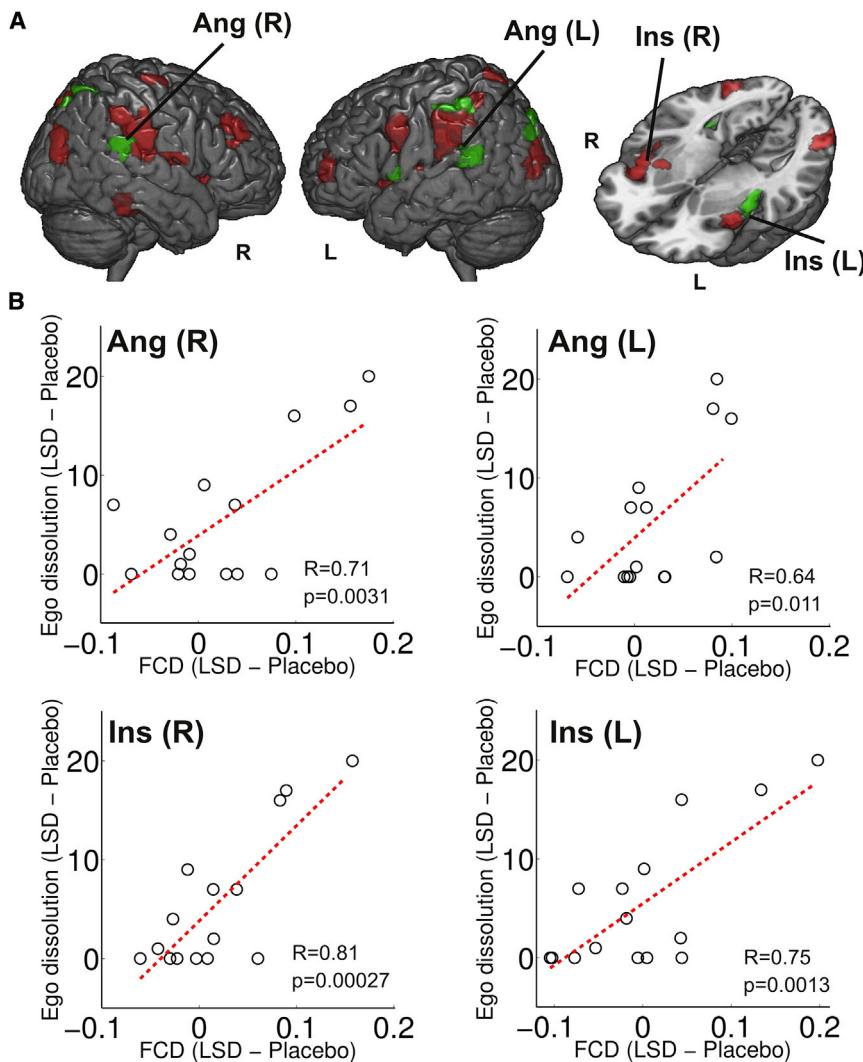
healthy subjects in the Human Connectome Project (HCP) dataset (<http://www.humanconnectomeproject.org>). These three RSNs (bilateral frontoparietal, default-mode, and salience networks) showed a significant overlap with FCD increases under LSD (Figure 1D) and

between the spontaneously fluctuating blood oxygen level-dependent (BOLD) signal at each region of interest and the time series from all remaining ROIs. Thus, high FCD values correspond to regions whose activity is strongly correlated to that of the rest of the brain, whereas activity in regions with low FCD values is weakly correlated to that of the rest of the brain. The average FCDs measured under LSD and placebo are shown in Figure 1A as a 3D rendering on top of a gray-matter surface. Histograms depicting the distribution of FCD values across all ROIs were obtained for both conditions. In the LSD condition there was a tail of highly coupled regions that was less prominent in the placebo condition (Figure 1B). FCD values were globally increased under LSD compared with placebo (Figure 1B inset).

The increases in global connectivity under LSD were observed in predominantly in frontal, parietal, and inferior temporal cortices, as well as in the bilateral thalamus. In Figure 1C we present a rendering of these effects together with the outline of three resting state networks (RSNs) obtained by applying independent component analysis [16] to resting-state data from 35

subjects in the HCP dataset. These three RSNs (bilateral frontoparietal, default-mode, and salience networks) showed a significant overlap with FCD increases under LSD (Figure 1D) and have been implicated in the action of other psychedelics [5, 8]. Additionally, we found a significant overlap between FCD increases under LSD and the distribution of 5-HT_{2A} receptors (the key site of action of psychedelic drugs [4]), obtained using positron emission tomography (PET) [6], as well as with FCD increases observed under psilocybin (same data and pre-processing as reported in [15]) (Figure 1D, right). We did not observe significant overlap between FCD increases and the distribution of other serotonin receptors (i.e., the 5-HT_{1A} and 5-HT_{1B} receptors).

Subsequently, we correlated the magnitude of regional FCD increases observed under LSD with the intensity of ego dissolution reported by the participants (LSD minus placebo) across all ROIs. Regions surviving correction for multiple comparisons included the bilateral temporo-parietal junction (angular gyrus) and the bilateral insular cortex (red rendering in Figure 2A). The specificity of this finding was assessed by also correlating all other VAS (visual analog scale) scores with FCD increases under LSD. Importantly, ego dissolution was the only subjective rating that survived this multiple-comparisons correction (see



[Figure S2](#) for more information on VAS and ASC [altered state of consciousness questionnaire] scores). In the green rendering in [Figure 2A](#), we identify those regions presenting correlations with ego dissolution scores (corrected for multiple comparisons) and uncorrelated to all other VAS scores (at a level of $p < 0.05$, uncorrected). Scatterplots of FCD versus ego dissolution are shown in [Figure 2B](#) for four example regions located in the left/right angular gyrus and insula. These regions were selected based on their overlap with the corresponding Automated Anatomical Labeling (AAL) atlas regions and their association with self-awareness [11, 12, 17, 18]. Scatterplots of FCD versus the other five VAS scores are provided in [Figure S4](#), and plots for four additional regions are provided in [Figure S3](#).

The FCD increases indicated that the overall global connectivity of the regions in [Figure 1C](#) increased under LSD relative to placebo. Next, we asked which areas of the brain became especially more engaged with these highly globally connected brain areas under LSD. To do this, we divided the FCD difference map ([Figure 1C](#)) into four components: a frontal seed (comprising parts of inferior, middle, and superior frontal gyri),

Figure 2. FCD Increases Correlate with Subjective Reports of Ego Dissolution

(A) Brain regions where a significant ($p < 0.05$, two-tailed, FDR-controlled for multiple comparisons) correlation between FCD and subjective reports of ego dissolution (LSD minus placebo) was found are colored in red. Brain regions where none of the other VAS scores correlated with FCD at $p < 0.05$, two-tailed, uncorrected (i.e., regions presenting the most selective correlations between FCD increases and ego dissolution scores) are colored in green.

(B) Association between FCD increases and reports of ego dissolution in four example ROIs (bilateral angular gyrus and insular cortex). See also [Figures S2 and S3](#).

a parietal seed (bilateral temporo-parietal junction/angular gyrus), the precuneus, and the bilateral thalamus. Seed-based regression analyses were subsequently conducted based on each of these four seeds (as the independent variables)

[Figure 3](#) displays difference maps with the regions becoming more coupled with four FCD-determined seeds (left panel) under LSD relative to placebo. In all four cases, sensory cortices were implicated (right panel). This result was further confirmed by repeating the permutation analysis [15] conducted for the FCD map ([Figure 1D](#))—yielding a significant overlap between the difference maps and four HCP-derived RSNs: a sensorimotor RSN spanning the pre- and post-central gyri, two visual RSNs (medial and

lateral), and an auditory RSN encompassing the superior temporal cortex (including the primary auditory cortex in the Heschl's gyrus). For comparison, the contour of these RSNs is overlaid with the maps of statistically significant regions in [Figure 3](#) (right panel).

Next, we evaluated whether LSD only scaled the magnitude of the coupling or also rearranged connectivity patterns in the brain, independently of the coupling strength. To do this, we studied the modularity of whole-brain functional connectivity networks having the ROIs as nodes. In the present context, modularity measures how well the brain can be parcellated into modules having dense within-module and sparse between-module connectivity [19]. Based on the observation of increased between-network connectivity under LSD ([Figure 3](#)), as well as previous findings with other psychedelics [20], we predicted that there would be a decrease in brain modularity under the drug, indicating a reduction in the separation of intrinsic brain networks. As shown in [Figure 4A](#), this prediction was supported over an extended range of functional network link densities (ratio of the number of binary connections present in the network to the maximum possible number of connections; see

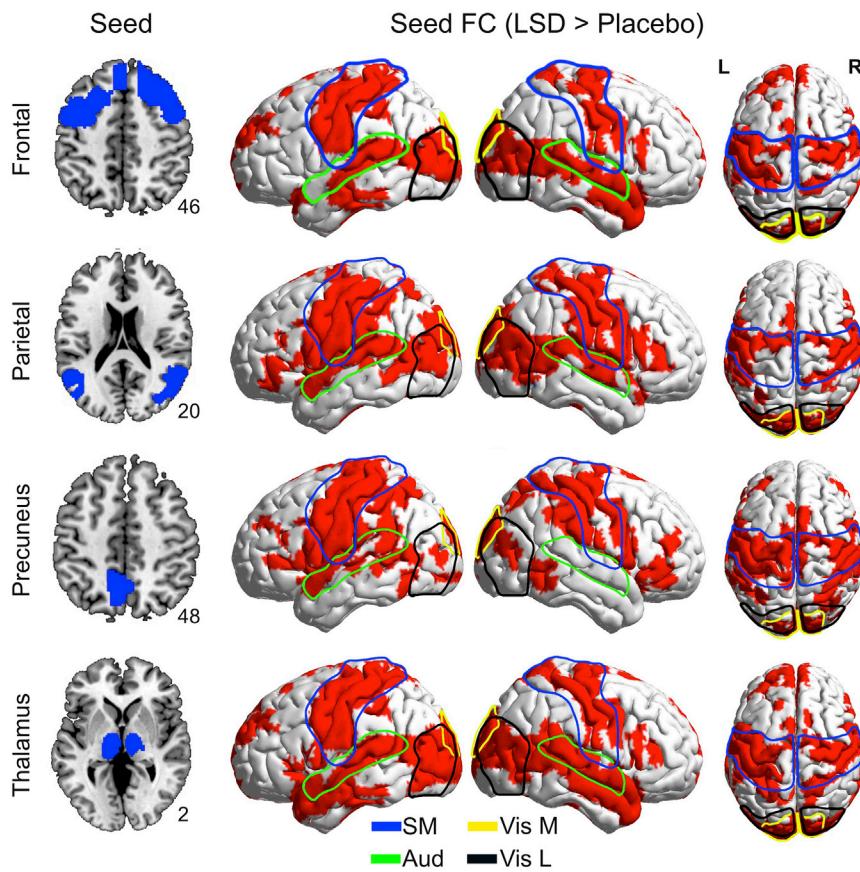


Figure 3. LSD Increases Between-System Functional Connectivity

Results of seed correlation analyses based on four ROIs (leftmost column) defined from the map of significant FCD increases (Figure 1C). In the three columns at right, regions in red indicate significantly higher connectivity ($p < 0.05$, two-tailed t test, FDR-controlled for multiple comparisons) with the seed (leftmost column, in blue) under LSD relative to the placebo. A permutation test revealed that only four RSNs present a significant ($p < 0.05$, Bonferroni-corrected for multiple comparisons) overlap with the functional connectivity increases under LSD: the sensorimotor (SM), auditory (Aud), visual medial (Vis M), and visual lateral (Vis L) RSNs. The contour of these RSNs is jointly rendered with the maps of functional connectivity changes. See also Figures S1 and S3.

DISCUSSION

Taken together, the present results indicate that LSD enhances global and between-module communication while diminishing the integrity of individual modules, and that this effect is mediated by the brain's key integration centers such as those that are rich in 5-HT_{2A} receptors. These results invite comparisons with those of our previous functional imaging studies with psilocybin, a related

compound and another serotonergic psychedelic. For example, in [5] we reported decreases in functional connectivity between anterior and posterior nodes of the DMN under psilocybin, and in [22] and [23] we suggested that decreased within-network integrity was a general property of psychedelics. Furthermore, two subsequent reports detailed increased between-RSN connectivity under psilocybin [20, 24], matching the directionality of the effects found here with LSD. Indeed, re-analysis of our previously acquired psilocybin fMRI data revealed FCD increases in regions similar to those observed here with LSD (Figures 1D and S1). Importantly, despite overlap with the default-mode, fronto-parietal, and salience networks, the results of the current FCD analysis were not constrained a priori to these or any other specific RSN.

Intriguingly, a formal analysis revealed significant overlap between the regions of increased global connectivity under LSD and those that express the 5-HT_{2A} receptors in especially high concentrations. 5-HT_{2A} receptor agonism is known to increase cell excitability (in particular of layer V pyramidal neurons) [25], which may result in higher metabolic demands. Increased glucose metabolism in frontal, temporal, and subcortical regions has been reported for serotonergic psychedelics, and these increases correlate with subjective reports of ego dissolution [26]. Glucose metabolism is also known to covary with the density of functional connections [27], thus establishing a possible connection between the FCD increases observed here and 5-HT_{2A} receptor-mediated changes in neural excitability.

Supplemental Experimental Procedures. In Figure 4B, we show the modules identified by the modularity optimization algorithm. We also computed the participation coefficient of each node (measuring how much each node communicates across modules relative to how much they communicate within their own module [19]) and observed increased participation coefficients in frontal and midline regions (Figure 4C) overlapping with those in Figure 1C, suggesting that these areas serve as conduits for increased between-module communication under LSD.

Finally, we investigated changes in the level of integration between highly coupled regions by means of the so-called "rich-club" coefficient $\Phi(k)$. This metric calculates the ratio of links between nodes of degree (i.e., the number of attached links) higher than a certain number (k) over the maximum possible number of links between them, and it is normalized by the same metric computed after degree-preserving randomization of the network [21]. In Figure 4D we show that the rich-club coefficient is higher under placebo than LSD, indicating that LSD decreases the level of (preferential) communication between the brain's dominant hub regions. These hub regions are found within a single module (corresponding to primary sensory areas; green module in Figure 4B) as revealed by the k-core of the LSD and placebo networks (with $k = 100$), defined as the smallest subset of nodes with degree at least equal to k (see Figure 4E). Thus, LSD enhances between-module integration at the expense of impairing within-module communication of highly coupled nodes.

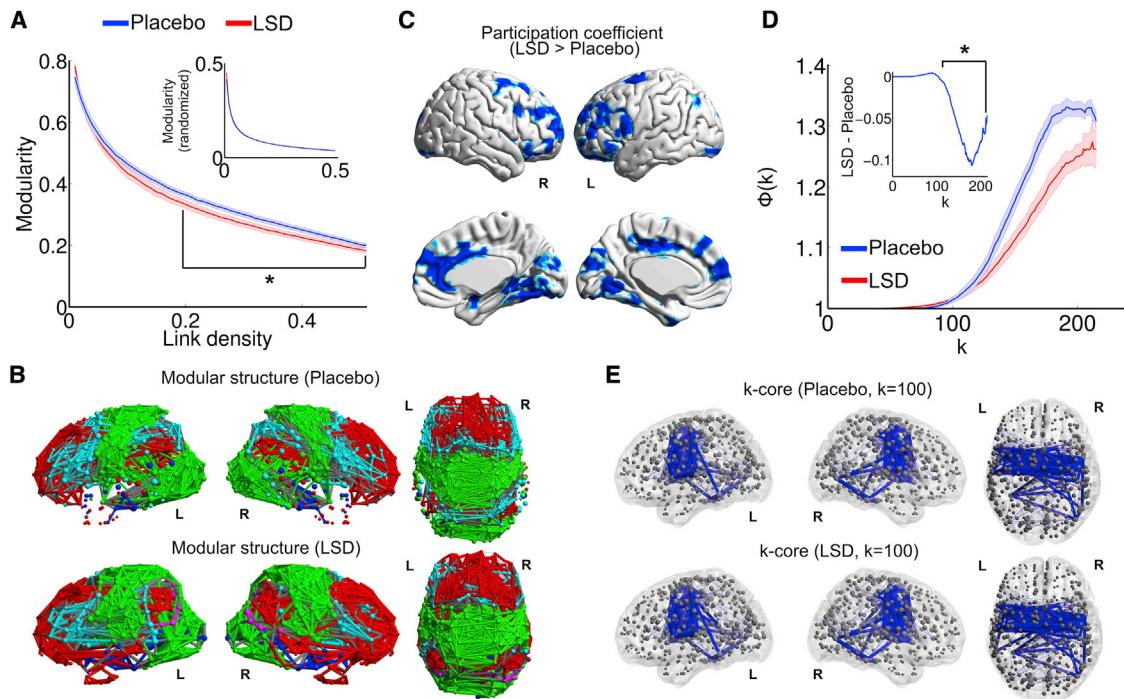


Figure 4. LSD Increases Global Integration

- (A) Modularity versus link density for the LSD and placebo conditions (mean \pm SEM, * p < 0.05, two-tailed t test, FDR-controlled for multiple comparisons). The inset shows the same for networks after degree-preserving randomization (no significant differences were found).
(B) Rendering of the modules identified at a reference link density of 0.3, for the placebo (top) and LSD (bottom) conditions.
(C) Regions presenting increased participation coefficient in LSD versus placebo (link density = 0.3, p < 0.05 two-tailed t test, FDR-controlled for multiple comparisons).
(D) Normalized rich-club coefficient $\phi(k)$ for LSD and placebo. The inset shows the difference between both conditions (mean \pm SEM, link density = 0.3, * p < 0.05, two-tailed t test, FDR-controlled for multiple comparisons).
(E) k-cores ($k = 100$) for placebo (top) and LSD (bottom) conditions. See also Figure S4.

Electroencephalography (EEG) studies performed during the 1950s and 1960s reported broadband decreases in oscillatory power under LSD [28], and magnetoencephalography recently revealed diminished power in a broad range of frequency bands after psilocybin infusion [23]. 5-HT_{2A} receptor-mediated oscillatory desynchronization can be traced to an uncoupling of layer 5 pyramidal cell firing from local field potential oscillations [29], suggesting that dysregulating the firing of these neurons is critical. In the human cortex, decreases in alpha power after psilocybin infusion are particularly marked, and decreased alpha in the posterior DMN (precuneus/posterior cingulate cortex) correlates with the intensity of ego dissolution [22]. A number of multimodal EEG-fMRI studies have now revealed an inverse correlation between global functional connectivity and power in the alpha band [30–32], which reconciles these electrophysiological observations with our findings of increased global connectivity in high-level association areas under both LSD and psilocybin. Alpha oscillations have been hypothesized to inhibit or regulate task-irrelevant (i.e., “spontaneous” or “ongoing”) neural processes [33]; thus, findings of reduced alpha under psychedelics suggest that these drugs could reduce this inhibition (i.e., be disinhibitory). It must be noted, however, that alpha oscillations are linked to a number of cognitive processes (e.g., attention, memory, executive control, and conscious access)

[34], and the hypothesized disinhibition cannot be directly inferred from the present results.

The areas of the brain that displayed increased global connectivity under LSD have different functional roles. The frontoparietal cortex is implicated in conscious information access [35], and its activity is suppressed in some states of diminished conscious awareness (such as seizures or deep sleep) [36], even though an unequivocal link between frontoparietal activity and the conscious state is lacking. Different DMN components perform functions related to self-consciousness: activity in the precuneus correlates with self-reflection processes and autobiographical memory retrieval [37], while the activation of temporo-parietal junctions is typical of out-of-body experiences [17]. The bilateral insular cortex is related to self-awareness [18], as well as to the processing of emotional information [38], that could also play an important role in the psychedelic experience. One intriguing possibility is that increased cross-talk between these networks and other brain systems underlies the experience of ego dissolution under LSD. This scenario is supported by our observation of positive correlations between increased FCD in the bilateral temporo-parietal junction and insular cortex and subjective reports of ego dissolution. Furthermore, we observed that the increases in global connectivity in these high-level regions particularly involved sensory areas. This increased communication between

high-level (association) and lower-level (sensory) cortices might represent a collapse in the normal hierarchical organization of the brain [22] such that the boundaries between lower-level systems anchored to the external world and higher-level systems operating more autonomously from sensory information become blurred. It is intriguing to speculate whether this blurring of boundaries and putative expansion of the “global workspace” [35] are related to the blurring of ego boundaries and the experiences of ego dissolution and “expanded awareness” reported in relation to psychedelics.

It is deserving of mention that our exploratory imaging analysis revealed significant (corrected) correlations with only one (out of six) VAS items, i.e., the one that enquired about feelings of ego dissolution. That the results of these exploratory whole-brain analyses correlated selectively with ego dissolution may be significant, as it suggests that this phenomenon is important [7] and dependent on changes that implicate the whole of the brain rather than just specific functional modules. It remains possible, however, that other aspects of the psychedelic experience (e.g., visual hallucinations) may depend on changes in the functioning of a particular module (e.g., the visual cortex), and this is something that we intend to investigate in the future.

As mentioned above, the quality of consciousness under psychedelics is frequently referred to as “expanded” [22]. It is reasonable to infer, therefore, that the neurophysiology of the psychedelic state will contrast with that of states of “diminished consciousness,” such as deep sleep or general anesthesia. Our results support this inference on many levels. As discussed above, increased frontoparietal FCD under LSD suggests higher metabolism in these regions, whereas unconscious states are generally characterized by diminished frontoparietal metabolism and connectivity [36]. Deep sleep, for instance, presents decreased density and efficiency of frontoparietal functional connections [39]. Both sleep and anesthesia are characterized by a breakdown of global functional integration, resulting in increased modularity values [40, 41], whereas we observed decreased modularity values under LSD, reflecting enhanced between-module cross-talk. Broadly speaking, this study’s results are consistent with the previous hypothesis that the psychedelic and unconscious states occupy polar-opposite ends of a spectrum of conscious states, defined by their level of entropy or randomness [22]. This hypothesis can now be updated to state that the brain’s level of modularity (low modularity being characteristic of random and disordered networks [19]), during a particular period of time (e.g., the duration of resting-state scan), is predictive of the subjective quality of consciousness that is experienced during that period. Further work is required to develop our characterization and subsequent quantification of the subjective nature of conscious states [42]; however, the present measure of ego dissolution can be viewed as a start in this direction.

Some limitations of our study must be acknowledged. First, while we attempted by all available means to reduce the impact of head motion in our results and to show that our results cannot be attributed to motion confounds (see section “Motion” in the [Supplemental Experimental Procedures](#)), significant differences in head motion persisted between conditions. Second, the particularly strict criteria used to combat motion artifacts reduced our original sample of 20 subjects to a smaller sample

of 15 “clean” datasets. Third, our analysis of ego dissolution was based on a single numerical report by experienced psychedelic drug users; future studies should attempt a more thorough characterization of the subjective dimension of this experience. Finally, since the participants were experienced psychedelic drug users, it is more likely that they could differentiate the LSD from the placebo, potentially leading to demand characteristics. It would be interesting to repeat these analyses in psychedelic-naïve participants to test whether past use of psychedelics can be predictive of the reported effects, although we failed to observe any correlations between past use and the above-reported effects of LSD in the present study.

In conclusion, the present study aimed to explore one of the most remarkable and least understood domains of the psychedelic experience, known both colloquially and academically as “ego dissolution.” It revealed an increase in global integration within the brain (but a decrease in within-module integrity), seemingly mediated by high-level cortical association regions that are rich in 5-HT_{2A} receptors, as well as the thalamus. Importantly, the increases in global integration in cortical association regions selectively correlated with subjective ratings of ego dissolution. These results help to inform not only on the neurobiology of the psychedelic experience but on a fundamental aspect of human consciousness, namely the sense of possessing a coherent “self” or “ego” that is distinct from others and separate from the external environment. Further work is required to develop these insights and explore other interesting aspects of the phenomenology of the psychedelic experience. Finally, the present study reinforces the view that, conducted with appropriate care, human research with psychedelic drugs is safe and can provide valuable insights in human neuroscience.

EXPERIMENTAL PROCEDURES

This study was approved by the National Research Ethics Service Committee London – West London and was conducted in accordance with the revised Declaration of Helsinki (2000), the International Committee on Harmonisation Good Clinical Practices guidelines, and the National Health Service Research Governance Framework. Imperial College London sponsored the research, which was conducted under a Home Office license for research with Schedule 1 drugs. Detailed experimental procedures (including information on subject recruitment, experimental design, data acquisition, and data analysis) can be found in the [Supplemental Information](#).

SUPPLEMENTAL INFORMATION

Supplemental Information includes four figures and Supplemental Experimental Procedures and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2016.02.010>.

AUTHOR CONTRIBUTIONS

E.T. analyzed the data, produced all figures, and wrote the manuscript. L.R. contributed to study design, analyzed the data, and wrote the manuscript. M.K. contributed to study design, recruitment of volunteers, and data analysis. C.O. contributed to data analysis. S.D.M. contributed to study design and coordination. K.M. contributed to data analysis. H.L. contributed to data analysis and edited the manuscript. R.L. contributed to study design and edited the manuscript. J.M. contributed to data analysis. N.C. and E.B. contributed to data analysis and edited the manuscript. T.W. and M.B. helped perform the research, cared for participants, administered the LSD, and served as

medical/psychiatric cover for the study. A.F. was instrumental in initiating the research and edited the manuscript. D.J.N. advised on the study design and implementation and edited the manuscript. R.C.-H. designed and led the study, oversaw recruitment, contributed to data analysis, and edited the manuscript.

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E.B. is employed half-time by University of Cambridge and half-time by GlaxoSmithKline; he holds stock in GlaxoSmithKline.

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